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Follow-up, treatment, and reinfection rates among asymptomatic *Chlamydia trachomatis* cases in general practice

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SUMMARY

Background: *Adequate treatment and follow-up of patients is essential to the success of a screening programme for* Chlamydia trachomatis. *There has been a lack of data on follow-up, confirmation of infections, and reinfection rates among asymptomatic patients in general practice.*

Aim: *To study the rates of diagnostic confirmation of* C trachomatis *infection, successful treatment, and reinfection one year after cases were detected in a screening programme for asymptomatic infections.*

Design of study: *Prospective cohort study.*

Setting: *Fifteen general practices in Amsterdam, The Netherlands.*

Method. *One hundred and twenty-four patients with asymptomatic* C trachomatis *infections were requested to provide a cervical or urethral swab and a urine specimen, for the purpose of diagnostic confirmation before being treated. One year after the first screening, all of the patients were invited for a second screening. All samples were tested using the ligase chain reaction (Abbott Laboratories, Chicago, USA).*

Results: *Out of 124 patients, 110 (89%) attended the scheduled appointment for diagnostic confirmation and treatment; 92 (84%) of them were confirmed to be positive and received treatment. At the second screening a year later, none of the 56 patients who had received treatment and who had been screened a second time were reinfected.*

Conclusion: *No asymptomatic patients were found to have reinfections with* C trachomatis *one year after diagnostic confirmation and treatment. This underlines the effectiveness of the screening and treatment strategy.*

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Introduction

GENITAL infection with *Chlamydia trachomatis* is the most prevalent sexually transmitted infection in The Netherlands, as well as in other industrialised countries.[1] Since it causes no or few symptoms, many infections remain undetected. An untreated infection in women may lead to pelvic inflammatory disease (PID), and at a later stage to infertility, ectopic pregnancy, and chronic abdominal pain.[2] Infected women can pass the infection on to their children at birth.[4] Complications in men are less severe, but the screening and treatment of men is important in limiting the spread of the infection.

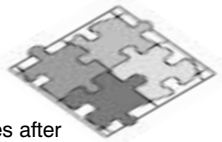
Scholes *et al* have shown that screening for asymptomatic infections in women leads to a reduction of 56% in the incidence of PID.[2] To date, most screening programmes have been opportunistic, aimed at patients attending various types of clinics or in specific high-risk groups. The introduction of sensitive DNA detection methods on non-invasively collected specimens, such as urine,[5-6] and the use of posted samples obtained at home enables screening beyond the traditional settings.[7-8]

Various pilot studies have been conducted in general practice throughout Europe to detect asymptomatically infected individuals.[9-11] Adequate treatment and follow-up of patients is essential to the success of any screening programme. *C trachomatis* infections can be treated effectively with a single dose of azithromycin.[12] However, reports from clinics for sexually transmitted diseases (STDs) suggest that the follow-up of infected individuals may not always be successful.[13] However, this may not be applicable to asymptomatically infected patients in general practice where the follow-up rates may be better, since there is often a longstanding relationship of trust with the physician.

Another important factor in the success of a screening programme is the number of reinfections that occur during follow-up, which determines how often screening should be repeated in a certain setting. Research in schools and STD clinics in the United States has reported reinfection rates varying from between 6% and 15% within one year.[14-16] This rate is probably lower in the general population, although no specific data are available.

The main objective of our research was to study the rates of diagnostic confirmation of *C trachomatis* infection, successful treatment, and reinfection one year after asymptomatic infections were detected in a screening programme in general practice.

HOW THIS FITS IN



What do we know?

No specific data were available on the success of follow-up and reinfection rates after screening for asymptomatic infections in general practice.

What does this paper add?

In this study it was shown that, with adequate follow-up, the reinfection rates among asymptomatic cases within one year are low.

Method

Between January 1997 and December 1998, 124 men and women were screened and tested positive for an asymptomatic *C trachomatis* infection. All cases were detected in a study of 11 005 men and women between the ages of 15 and 40 years of age, who were randomly selected from the computerised registers of 15 general practices in Amsterdam and invited to participate in a large screening programme for asymptomatic *C trachomatis* infection. All practices had been selected based on previous research experience with the co-ordinating research institute (EMGO Institute). The practices were spread throughout the city, such that all districts of Amsterdam were represented in the study. Participants in the screening were requested to return by post a urine specimen obtained at home and a completed questionnaire containing questions on demographic variables, current urogenital symptoms, history of STDs, and sexual behaviour.[9] The participation rate was 33% for men and 51% for women. All participants were considered to be asymptomatic, even though mild genitourinary complaints were reported by a large proportion of the screened population. However, these symptoms were not recognised as signs of infection and, as a consequence, patients did not consult a physician and did not believe themselves to be at risk of an infection.

Participants were compared with non-participants on several demographic variables. Participants were found to be similar to non-participants with regard to marital status, type of health insurance and age. However, participants were more likely than non-participants to be of Dutch origin.[9] The prevalence of infection was 2.4% among men and 2.8% among women. The screening results were reported back to the general practice in which the patient was registered. The general practitioner (GP) was requested to invite all infected patients to attend an appointment at the surgery. They received either a written invitation or a telephone call, depending on the preference they had stated in the questionnaire. They were informed that an infection had been found and that it was very important to make an appointment for diagnostic confirmation and eventual treatment. Those who did not respond to the initial notification within two weeks received a reminder telephone call from their physician.

At the time of the visit to the surgery, patients were invited by the GP to participate in the follow-up study, as well as a partner notification procedure. They were assured that they would receive adequate treatment, regardless of whether or not they decided to participate.

A cervical swab was taken from female patients and a urethral swab from male patients, and a second urine specimen was collected. The screening results were considered to be confirmed if at least one of the two specimens was again positive for *C trachomatis.* The treatment consisted of a single dose of 1000 mg azithromycin, or erythromycin for pregnant women (4 × 500 mg for five days). Partners were notified, as described elsewhere.[9,17]

Detection of C trachomatis

All samples obtained during the study were tested for the presence of *C trachomatis* DNA by means of the ligase chain reaction (LCR) test (Abbott Laboratories, Chicago, Illinois, USA) in the laboratory of the Department of Pathology of the Academic Hospital Vrije Universiteit. Tests were performed according to the instructions of the manufacturer and the results of all tests were reported back to the practice where the patient was registered.

Test of cure

Patients were requested to return four weeks after receiving treatment, when another urine sample was obtained. If the patient tested positive again, it was ascertained whether the patient had taken the medication and whether current sexual partners had been tested and treated. If not, the patient was instructed to take the treatment and to notify partners that they should receive adequate treatment. If it was likely that the positive test result was owing to treatment failure, a seven-day course of doxycycline was prescribed and the patient was requested to come back again one month later.

Follow-up after one year

One year after the patients were last seen by the GP and tested negative, or one year after the estimated date if the patient had not had a test of cure, a package for the follow-up screening test was sent to their current home address. All the correspondence was sent from the practice by the GP to ensure confidentiality and anonymity of the patients. The package contained an information leaflet, a short questionnaire, a urine container and a disposable glove. The patient was requested to collect a urine sample and to answer seven questions on the questionnaire about current complaints, number of new sexual partners, treatment, and partner notification after the last screening. They were requested to send the coded urine sample and questionnaire to the Department of Pathology in a prepaid envelope which was included in the package. A single written reminder was sent by the GP if the package had not been returned within four weeks of the posting date. The test results were reported back to the general practice where the patient was registered. General practitioners were requested to provide adequate follow-up and treatment, if indicated.

Statistical analysis

The percentage of patients contacted for diagnostic confirmation and treatment was determined, and determinants of non-attendance were investigated. The results of the confirmatory tests and factors correlating to the discrepancy of

these results with the original screening test were evaluated. The percentages of participation in the test of cure and the rate of successful treatment were determined.

The participation rate and rate of reinfection with *C trachomatis* (percentages) were determined after one year. The data were analysed using the SPSS package version 7.5.2. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all associations. Where appropriate, χ^2 tests were used.

Results

Figure 1 shows a flow-chart of the follow-up study. Of the 124 cases detected in the initial screening, 110 (89%) responded to the invitation for an appointment with their GP and were thus eligible to participate in the follow-up study. None of those who did not respond to the invitation gave a reason for not attending. All eligible patients agreed to participate in the first part of the follow-up study, the diagnostic confirmation test and the test of cure. Being of Surinam/Antillean origin was positively associated with non-attendance. Patients under 25 years of age, patients with no current genitourinary complaints, and patients who had completed less than 16 years of education seemed to have lower attendance rates. However, confidence intervals of all associations were wide and included a value of 1.

Ninety-two (84%) of the 110 patients who were tested again were confirmed to be positive and were treated for *C trachomatis* infection. No associations were found with young age, gender, reported complaints, Surinam/Antillean origin, multiple sexual partners, having had an STD, inconsistent condom use, level of education or marital status (data not shown).

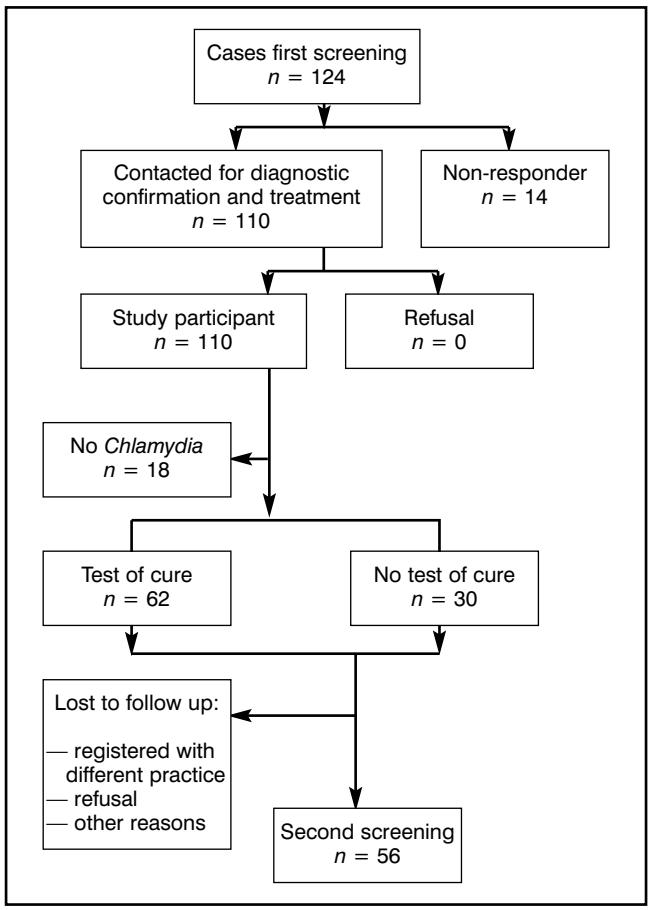


Figure 1. Flow chart of follow-up cases with an asymptomatic Chlamydia trachomatis *infection after screening.*

All treated patients were requested to return for a test of cure. Sixty-two (67%) of the 92 patients who had been treated participated in the test of cure. No associations were found with young age, gender, reported complaints, Surinam/Antillean origin, multiple sexual partners, history of STD, inconsistent condom use, level of education or marital status (data not shown). Five (8%) patients were tested positive and were treated again for the infection. All of them reported that they had complied with the initial treatment.

One year after treatment, the 92 treated patients were invited to participate in the second screening. Fifty six (61%) participated. Of the non-participants, two explicitly refused further participation in the study and nine could not be contacted because their current address was unknown. The rest did not participate for other or unknown reasons. Patients who had had a test of cure participated in the second screening more frequently than those who had not (odds ratio = 5.0 [95% CI = 2.4 to 10.1]). Age at the time of the first screening, gender, reported complaints, Surinam/Antillean origin, multiple sexual partners, having had an STD prior to the first screening, inconsistent condom use, level of education and marital status were not associated with participation (Table 2). Of the patients participating in the second screening, 53 (95%) reported that they had been treated for infection after the initial screening. Thirty eight (68%) stated that they were certain that all their sexual partners had been notified and tested after the initial screening. Fourteen (25%) patients reported that they had a new sexual partner since the last screening. None of the participants in the second screening tested positive for *C trachomatis* infection.

Discussion

Attendance

In this study we have described what happens after a positive screening test for an asymptomatic *C trachomatis* infection. Of all the positive patients, 11% did not respond to the invitation for an appointment for diagnostic confirmation and treatment. This rate is similar to the rates reported in other settings.[13,18,19] Attendance for diagnostic confirmation and treatment is an important factor that must be taken into consideration in the evaluation of a screening programme because it relates directly to its effectiveness, particularly in terms of cost. This is often neglected.[20,21] Untreated patients remain at risk of developing complications, such as PID, tubal factor infertility, and ectopic pregnancy[2,22] and risk spreading the infection to their sexual partners.

To increase the number of patients treated, the computer files of the patients who did not attend could be marked, so that the GP is reminded of the positive screening test result the next time this patient shows up at the surgery for any reason. The GP would then have the opportunity to discuss the likelihood of infection with the patient during the visit, and to offer diagnostic confirmation and eventual treatment. Attendance among patients of Surinam/Antillean origin was lower than among patients of other origins. This finding may

Table 1. Determinants associated with the attendance for diagnostic confirmation and treatment after a positive screening test result for asymptomatic Chlamydia trachomatis *infections in general practice.*

Determinant	Prevalence of determinant (%)		Crude OR (95% CI)
	Non-participants (n = 14)	Participants (n = 110)	
Male sex	29	35	1.10 (0.31–1.80)
Age ≤25 years	42	28	0.54 (0.16–1.80)
Surinam/Antillean origin	50	16	0.19 (0.05–0.66)
Married or cohabiting	50	66	1.90 (0.59–6.50)
Having at least 16 years of education	83	66	0.25 (0.05–1.20)
Inconsistent condom use	46	65	2.20 (0.62–7.70)
History of STD	18	19	1.00 (0.21–5.20)
Current genitourinary complaints[a]	67	38	0.31 (0.09–1.10)
Changing sexual contacts	36	24	0.56 (0.15–2.10)

[a]Mild genitourinary complaints were reported by a large proportion of the population. However, symptoms were not recognised as a sign of infection and a physician was not consulted; these cases were therefore considered to be asymptomatic.

Table 2. Determinants[a] associated with non-participation in a second screening one year after cases were detected in a screening programme for asymptomatic Chlamydia trachomatis *infections in general practice.*

Determinant	Prevalence of determinant (%)		Crude OR (95% CI)
	Non-participants (n = 36)	Participants (n = 56)	
Male sex	48	28	2.40 (0.96–5.80)
Age ≤25 years	24	29	0.80 (0.46–1.70)
Surinam/Antillean origin	15	20	0.71 (0.22–2.30)
Married or cohabiting	61	65	0.84 (0.34–2.00)
Having at least 16 years of education	59	57	1.10 (0.42–2.60)
Inconsistent condom use	58	71	0.56 (0.23–1.40)
History of STD	25	18	1.50 (0.52–4.30)
Current genitourinary complaints	30	46	0.50 (0.20–2.00)
Changing sexual contacts	18	31	0.50 (0.17–4.00)

[a]Determinants as classified at the time of the first screening test.

be relevant for practice if it can be confirmed in future studies. It should be taken into account that it may be a chance finding, and may be owing to multiple comparisons used in the present study in an attempt to identify potentially relevant determinants of attendance.

Confirmation

In the present study, 18 of the positive screening tests could not be confirmed, suggesting that 16% of the positive screening tests were false positives. The specificity of the LCR test on urine is estimated to be around 99%.[5,7] In a low prevalence population, as in the present study,[9] this specificity may lead to a substantial number of false positives.

Given the potential consequences for a patient of positive test results, which may be inaccurate; e.g. the effect on relationships and the possible side effects of treatment, we recommend that in a controlled environment, such as a general practice surgery, the screening test result should be confirmed before offering treatment and notifying partners.

Test of cure

Five patients were still positive after the test of cure, although all of them reported that they had been treated. This finding could be explained by treatment failure or by reinfection of the patients by an untreated partner. However, most patients reported that they had only one steady partner, and the majority of these steady partners were contacted and treated for infection.[17] Another possible explanation is that the test detected non-viable DNA, although reports suggest that a period of four weeks should be enough to clear the infection after treatment.[23] It has to be noted that a routine test of cure is currently not included in the recommendations on the management of *C trachomatis* infections.[24,25]

Reinfection

No participants in the second screening were found to be reinfected, although the study population was considered to be at high risk of infection, based on the fact that they were diagnosed with an asymptomatic *C trachomatis* infection at the first screening. The absence of reinfections underscores the fact that the general population is at low risk of acquiring a *C trachomatis* infection.

A limitation of this study is that only 61% of the patients were screened a second time. Although no major differences were found among participants and non-participants of the second screening, it should be taken into account that possibly only those patients who lead more stable sexual lives participated.

Patients who did not have a test of cure — a determinant of participation in the second screening — could potentially

have suffered treatment failure. This could have led to higher estimated reinfection rates, since *C trachomatis* infection is assumed to persist if left untreated.[26]

Detection of *C trachomatis* in the second screening was based on an LCR test on urine. Various studies, which have been reported in the literature, found reduced sensitivities for the LCR test on urine, especially for women. The sensitivity on urine for women is estimated to be between 85% and 95%.[5-7] Based on this, some infections among the women who participated in the second screening could have been missed. At the same time, with a low incidence or prevalence of infection, as mentioned previously, some false-positive test results would be expected to occur. This was not the case.

Training

The GPs who participated in our study had only a small amount of specific postgraduate training for the follow-up of patients with chlamydial infection. In one session they were instructed on how to obtain a cervical or urethral swab and had the procedure for the follow-up explained. After the study it was often reported by the GPs that the consultations for diagnostic confirmation and treatment had been very demanding, especially since the infection was diagnosed unexpectedly in most patients. They stressed the need for specific training in how to present the test results and how to discuss the potential physical and social consequences of the infection. This result confirms findings from a qualitative study that staff outside specialised services may require guidance on providing support to women diagnosed with infection,[27] since health advisors have an important role in communicating the results, giving advice, and providing reassurance.[27,28] If screening were to be implemented, this should be an important element in the implementation strategy.

To summarise, no reinfections with *C trachomatis* were found among asymptomatic cases one year after diagnostic confirmation and treatment. Despite the small study size, this clearly underlines the effectiveness of the screening and treatment strategy and underscores the fact that the general population is at relatively low risk of acquiring a *C trachomatis* infection.

References

1. van de Laar MJW, Ossewaarde JM (eds). Sexually transmitted diseases in the Netherlands; update 1996. [in Dutch.] Bilthoven: RIVM Rapport 441500006, 1997.
2. Scholes D, Stergachis A, Heidrich FE, *et al.* Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med* 1996; **334:** 1362-1366.
3. Westrom L, Joesoef R, Reynolds G, *et al.* Pelvic inflammatory disease and fertility; a cohort study of 1844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis* 1992; **4:** 185-191.
4. Schachter J, Grossman M, Sweet RL, *et al.* Prospective study of perinatal transmission of Chlamydia trachomatis. *JAMA* 1986; **255:** 3374-3377.
5. van Doornum GJ, Buimer M, Prins M, *et al.* Detection of Chlamydia trachomatis infection in urine samples from men and women by ligase chain reaction. *J Clin Microbiol* 1995; **33:** 2042-2047.
6. Chernesky MA, Jang D, Lee H, *et al.* Diagnosis of Chlamydia trachomatis infections in men and women by testing first-void urine by ligase chain reaction. *J Clin Microbiol* 1994; **32:** 2682-2685.
7. Østergaard L, Møller JK, Andersen B, and Olesen F. Diagnosis of urogenital Chlamydia trachomatis infection in women based on mailed samples obtained at home: multipractice comparative study. *BMJ* 1996; **313:** 1186-1189.
8. Morré SA, van Valkengoed IGM, de Jong A, *et al.* Mailed, home-obtained urine specimens: a reliable screening approach for detecting asymptomatic Chlamydia trachomatis infections. *J Clin Microbiol* 1999; **37:** 976-980.
9. van Valkengoed IGM, Morré SA, van den Brule AJC, *et al*. Low diagnostic accuracy of selective screening criteria for asymptomatic Chlamydia trachomatis infections in the general population. *Sex Transm Infect* 2000; **76:** 375-380.
10. Macleod J, Rowsell R, Horner P, *et al.* Postal urine specimens: are they a feasible method for genital chlamydial infection screening? *Br J Gen Pract* 1999; **49:** 455-458.
11. Vuylsteke B, Vandenbruaene M, Vandenbalcke P, *et al.* Chlamydia trachomatis prevalence and sexual behaviour among female adolescents in Belgium. *Sex Transm Infect* 1999**; 75:** 152-155.
12. The Azithromycin for Chlamydial Infections Study Group. Martin DH, Mroczkowski TF, Dalu ZA, *et al.* A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. *N Engl J Med* 1992; **327:** 921-925.
13. Katz BP, Danos CS, Quinn TS, *et al.* Efficiency and cost-effectiveness of field follow-up for patients with Chlamydia trachomatis infection in a sexually transmitted diseases clinic. *Sex Transm Dis* 1988; **15:** 11-16.
14. Richey CM, Macaluso M, Hook EW. Determinants of reinfection with Chlamydia trachomatis. *Sex Transm Dis* 1999; **26:** 4-11.
15. Burstein GR, Gaydos CA, Diener-West M, *et al.* Incident Chlamydia trachomatis infections among inner-city adolescent females. *JAMA* 1998; **280:** 521-526.
16. Cohen DA, Nsuami M, Martin DH, Farley TA. Repeated school-based screening for sexually transmitted diseases: a feasible strategy for reaching adolescents. *Pediatrics* 1999; **104:** 1281-1285.
17. van Valkengoed IGM, Morré SA, van den Brule AJC, *et al.* Partner notification among asymptomatic Chlamydia trachomatis cases, by means of mailed specimens. *Br J Gen Pract* 2002; **52:** 352-354 (this issue).
18. Haddon L, Heason J, Fay T, *et al.* Managing STIs identified after testing outside genitourinary medicine departments: one model of care. *Sex Transm Inf* 1998; **74:** 256-257.
19. Monteiro EF, Harris J, Gilliatt P. A multidistrict audit on the management of Chlamydia trachomatis in genitourinary medicine clinics in Yorkshire. *Int J STD AIDS* 1997; **8:** 792-795.
20. Marrazzo JM, Celum CL, Hillis SD, *et al.* Performance and cost-effectiveness of selective screening criteria for Chlamydia trachomatis infection in women. Implications for a national Chlamydia control strategy. *Sex Transm Dis* 1997; **24:** 131-141.
21. Howell MR, Quinn TC, Gaydos CA. Screening for Chlamydia trachomatis in asymptomatic women attending family planning clinics. A cost-effectiveness analysis of three strategies. *Ann Intern Med* 1998; **128:** 277-284.
22. Stamm WE, Guinan ME, Johnson C, *et al.* Effect of treatment regimens for Neisseria gonorrhoeae on simultaneous infection with Chlamydia trachomatis. *N Engl J Med* 1984; **310:** 545-549.
23. Gaydos CA, Crotchfelt KA, Howell MR, *et al*. Molecular amplification assays to detect Chlamydial infections in urine specimens from high school female students and to monitor the persistence of chlamydial DNA after therapy. *J Infect Dis* 1998; **177:** 417-424.
24. Recommendations for the prevention and management of Chlamydia trachomatis infections, 1993. *Morb Mortal Wkly Rep CDC Surveill Summ* 1993; **42(RR-12):** 1-39.
25. Leicestershire Chlamydia Guidelines Group. Stokes T, Schober P, Baker J, *et al.* Evidence-based guidelines for the management of genital chlamydial infection in general practice. *Fam Pract* 1999; **16(3):** 269-277.
26. Dean D, Suchland RJ, Stamm WE. Evidence for long-term cervical persistence of Chlamydia trachomatis by omp1 genotyping. *J Infect Dis* 2000; **182:** 909-916.
27. Duncan B, Hart G, Scoular A, Bigrigg A. Qualitative analysis of psychosocial impact of diagnosis of Chlamydia trachomatis: implications for screening. *BMJ* 2001; **322:** 195-199.
28. Dixon-Woods M, Stokes T, Young B, *et al.* Choosing and using services for sexual health: a qualitative study of women's views. *Sex Transm Inf* 2001; **77:** 335-339.

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